Mitochondrial Biogenesis in the Acutely Injured Kidney

Mei Tran Samir M. Parikh

Division of Nephrology and Center for Vascular Biology Research, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Mass., USA

Key Words

Acute kidney injury · Biogenesis · Mitochondrial function · Mitophagy · Renal recovery

Abstract

Mitochondrial dysfunction within the tubular epithelium has been implicated in the pathogenesis of acute kidney injury. Inflammatory, ischemic, or toxic insults dysregulate mitochondrial dynamics, resulting in mitochondrial swelling, fission, and apoptosis. The coordinated processes of generating healthy mitochondria and clearing damaged organelles may contribute to the preservation and restoration of mitochondrial homeostasis. Emerging literature suggests that a master regulator of mitochondrial biogenesis, peroxisome proliferator-activated receptor- γ -coactivator-1 α (PGC-1 α), is highly expressed in the tubular epithelium of the healthy kidney, and its induction during the post-injury period may contribute to functional recovery from acute kidney injury.

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Mitochondria are dynamic organelles responsible for energy production in the cell. Although most proteins that comprise mitochondria are encoded in the nucleus, mitochondria have their own DNA (mtDNA) that is present in multiple copies per cell. Kidney tubular epithelial cells contain ample mitochondria to perform the energy-demanding processes of reabsorption and secretion.

Genetic inheritance of defective mtDNA underlies a subset of renal diseases often characterized by tubulopathy [1], which suggests that mitochondrial deficiencies are sufficient to produce clinically evident renal dysfunction.

Recent studies have implicated mitochondria within the tubular epithelium in initiating and determining the severity of kidney injury [2]. Electron microscopy has revealed that mitochondrial shape is altered and appeared swollen within the proximal tubule in toxic [3], ischemic [4], and septic [5] acute kidney injury (AKI) in humans and experimental animals. In mouse models of septic AKI, we have observed similar tubular vacuolization and prominent mitochondrial swelling [6]. Furthermore, biochemical analyses confirmed mitochondrial dysfunction as determined by decreased electron transport chain enzyme activity.

The processes of fission/fusion (collectively referred to as mitochondrial dynamics), mitophagy (i.e., the selective clearance of injured mitochondria through autophagy), and mitochondrial biogenesis contribute to the supply of healthy mitochondria within cells, and thus, to renal tubular resistance to ischemic, inflammatory, and toxic stressors (fig. 1). For example, dynamin-related protein (Drp1) and the pro-apoptotic protein Bax initiate mito-

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Fig. 1. In AKI, mitochondria within the proximal tubular epithelial cells undergo swelling, fission, and/or cell death. The clearance of damaged mitochondria (mitophagy) and generation of healthy organelles (mitochondrial biogenesis) may contribute to recovery.

chondrial fission and alter organelle morphology [7, 8]. Dysregulation of these proteins under stress leads to excessive mitochondrial fission and cellular death. Suppression of Bax or Drp1 preserved mitochondrial integrity and function, and reduced tubular apoptosis and injury in cellular and animal models of AKI. Similarly, induction of mitophagy by giving rapamycin has been shown to attenuate AKI following cisplatin treatment or renal ischemia-reperfusion injury, whereas drugs that slow this process may exacerbate AKI [9].

Mitochondrial biogenesis requires coordinated signaling between the nuclear and mitochondrial compartments. The peroxisome proliferator-activated receptor- γ coactivator-1 (PGC-1) transcriptional coregulators or-

chestrate much of this signaling by binding to nuclear receptors or transcription factors, effecting changes in metabolic processes such as fatty acid oxidation, oxidative phosphorylation, and reactive oxygen species (ROS) detoxification [10]. Members of the PGC-1 family are PGC-1 α , PGC-1 β , and PGC-1-related coactivator. In the healthy kidney, PGC-1 α expression is localized to the cortex and outer stripe of the medulla, corresponding to regions of mitochondrial abundance and intense solute transport activity [11]. Though PGC-1 α and PGC-1 β share responsibilities in regulating energy metabolism, PGC-1 α induction is more responsive to external and physiological stimuli [11, 12].

In our studies of the septic kidney, PGC-1 α expression was strongly correlated with the degree of renal dysfunction, whereas PGC-1 β expression was unaltered [6]. Following endotoxin injection, PGC-1 α expression declined along with renal function. This correlation was also evident in a surgical model of sepsis that recapitulates fecal peritonitis. After fluid resuscitation, mice recovered kidney function, and the expression of PGC-1 α and downstream mitochondrial genes rebounded to pre-injury levels. Global and proximal tubule-specific PGC-1 α knock-out mice were more susceptible to AKI and suffered persistent injury relative to control littermates. Studies by Funk and Schnellmann [13] corroborated these findings in myoglobinuric and ischemic models of AKI, where PGC-1 α and related electron transport chain gene expression were suppressed immediately following injury. Recovery of full renal function coincided with the restoration of mitochondrial proteins thereafter.

Upregulation of PGC-1 α and increased mitochondrial biogenesis may enhance recovery from renal injury. In primary human proximal tubular cells treated with tumor necrosis factor- α , PGC-1 α and associated mitochondrial gene levels were suppressed and oxygen consumption was reduced. Upon induction of PGC-1 α in these cells, normal oxygen consumption and respiratory chain function were reestablished [6]. Similar studies in rabbit proximal tubular cells revealed decreased ATP production, reduced mitochondrial function, and increased autophagy upon oxidant damage, all of which were reversed with PGC-1 α overexpression [14, 15].

AMP-activated protein kinase (AMPK) and sirtuin-1 (SIRT1), upstream of PGC-1 α , are also important modulators of energy metabolism and contribute to the mitochondrial biogenesis program. AMPK activates PGC-1 α via phosphorylation. Increasing AMPK levels in rats subjected to renal ischemia-reperfusion injury attenuated tubular necrosis, decreased nitrosative stress, and improved

Table 1. Induction of mitochondrial biogenesis in AKI

Model system	Experimental condition	Observations	First author
Primary rabbit RPTC	Oxidative stress: tert-butyl hydroperoxide	(1) Prior to injury, PGC-1 α overexpression accelerated cell injury and death (2) Following injury, PGC-1 α overexpression restored mitochondrial protein levels and promoted cellular respiration and ATP production	Rasbach [14, 15], 2007
Primary human RPTC	Acute inflammation: tumor necrosis factor- α	(1) PGC-1 α overexpression restored oxygen consumption and cellular respiration (2) PGC-1 α and related mitochondrial gene expression rebounded to pre-injury levels	Tran [6], 2011
Global and renal proximal tubule-specific PGC-1 α knockout mice	Endotoxemic AKI: lipopolysaccharide, cecal ligation perforation	(1) PGC-1 α and downstream mitochondrial gene levels rebounded as renal function recovered in control mice (2) PGC-1 α loss-of-function mice suffer from worse and persistent renal injury	Tran [6], 2011
Myoglobinuric AKI in rats Ischemic AKI in mice	Glycerol-induced myoglobinuric AKI Ischemia-reperfusion injury	PGC-1 α and related ETC gene expression were initially repressed, but restored when rodents fully recover kidney function	Funk [13], 2012
Ischemic AKI in rats	AMPK activation: AICAR	AICAR pretreatment attenuated injury and tubular necrosis, decreased nitrosative stress, and ameliorated renal function	Lempiainen [16], 2012
Primary rabbit RPTC	SIRT1 activation: SRT1720	SRT1720 given within 24 h of oxidant injury accelerated restoration of mitochondrial function, cellular respiration, and ATP production	Funk [17], 2010
Ischemic AKI in mice	β -Adrenergic agonist: formoterol	Formoterol after injury improved renal recovery, attenuated tubular necrosis, decreased KIM-1 levels, and restored mitochondrial protein expression and respiration	Jesinkey [18], 2014
ETC = Electron transport chain; KIM-1 = kidney injury molecule-1; RPTC = renal proximal tubular cells.			

renal function [16]. SIRT1 is an NAD⁺-dependent enzyme that deacetylates, and thereby activates, PGC-1 α . Schnellmann's group observed that the SIRT1 activator, SRT1720, induced PGC-1 α expression and mitochondrial biogenesis in an AMPK-independent manner [17]. SRT1720 administration to oxidant-injured cells, analogous to their previous work with PGC-1 α overexpression [14], improved mitochondrial function. The β -adrenergic agonist formoterol may also protect against ischemic renal injury by activating PGC-1 α [18].

While these studies with drugs and experimental small molecules strongly suggest that mitochondrial biogenesis may be a promising therapeutic target in AKI (table 1), caution is necessary. For example, AMPK, SIRT1, and β -adrenergic receptors have multiple effects on individual cells, let alone in a multiorgan context. Moreover, it has yet to be determined whether induction of mitochondrial biogenesis per se prior to AKI is beneficial or detrimental. Rasbach and Schnellmann [14] have noted that excess PGC-1 α prior to injury is deleterious rather than protective in proximal tubular cells. Although knockout mouse

data [6] suggest that increased mitochondrial biogenesis should accelerate healing, it remains formally possible that the presence of excess mitochondria at the time of insult may exacerbate injury through increased ROS generation. PGC-1 α regulates numerous aspects of cellular function, one of which is antioxidant defense [11]. Because mitochondria are necessary for efficient ATP generation, yet come with the risk of excess ROS generation, a transcriptional program that encodes both mitochondrial biogenesis and antioxidant defense downstream of PGC-1 α may have evolved to mitigate free radical damage while maximizing energy metabolism.

In summary, mitochondrial health is critical to kidney function. Mitochondrial dysfunction within the tubular epithelium is increasingly recognized as a pathogenic event in diverse forms of AKI. Recent experimental advances suggest that induction of mitochondrial biogenesis in the injury setting may restore mitochondrial function, bolster ATP production, and attenuate cell death. Therefore, targeting PGC-1 α and mitochondrial biogenesis may promote recovery of the acutely injured kidney.

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